REMARKS

Claims 1-16 were pending in the application. Claims 1- 4 have been canceled, claims 5, 7, 11, 12, and 15 have been amended, and claims 17-40 have been added by the present amendment. Accordingly, upon entry of the present amendment, claims 5-40 will be pending in the application.

The specification has been amended to correct a typographical error and a factual error. First, the specification has been amended at page 57, line 25, to change the misspelled name "Zhoa" to "Zhao." Second, Applicants have deleted a factual misstatement in the specification regarding Mathur *et al.*, "Journal of Macromolecular Science-Reviews In Macromolecular Chemistry and Physics," C36:405-430, 1996 ("the Mathur reference," copy enclosed). Applicants originally submitted the Mathur reference in an Information Disclosure Statement mailed on October 12, 2000. The Examiner enclosed a copy of the initialed Form PTO-1449 with the Office Action mailed April 25, 2001 (Paper No. 6).

Applicants have made two deletions with respect to the Mathur reference. First, Applicants have deleted the citation to the Mathur reference from the parenthetical after the following sentence:

> Michael-type addition to conjugated unsaturated groups can take place in good to quantitative yields at room or body temperature and in mild conditions with a wide variety of nucleophiles.

Page 57, lines 20-22. Second, Applicants have amended the sentence at page 57, line 25 – page 58, line 3, as follows:

> Conjugated unsaturated groups, such as vinyl sulfones (Pathak, supra) ~~or acrylamides (Mathur, supra)~~, have been used to link PEG or polysaccharides to proteins through Michael-type reactions with amino- or mercapto-groups.

The reason for these changes is that the Mathur reference does not disclose using acrylamides to link polyethylene glycol or polysaccharides to proteins through Michael-type reactions with amino or mercapto groups. Rather, the Mathur reference discloses polymerizing a precursor component containing an acrylamide in the presence or absence of another precursor component using redox polymerization, radiation-induced polymerization (*e.g.*, γ-ray-induced polymerization), or free-radical crosslinking. The Mathur reference also discloses polymerizing precursors containing acrylic acids and/or precursors containing methacrylic acids using photoinduced polymerization, redox polymerization, radiation-induced polymerization, or free-radical crosslinking. All of the

polymerization reactions disclosed in the Mathur reference are initiated by the formation of free radicals. The free radicals propagate through the carbon double bonds of the precursor components resulting in a chain reaction of precursor components and the formation of a polymerized gel (see, for example, page 408, lines 2-6 and 22-24). The Mathur reference does not disclose, teach, or suggest nucleophilic addition reactions between a nucleophile and a conjugated unsaturated group.

Claim 5 has been amended to correct a typographical error. Support for the amendment of claim 5 is found throughout the application as filed, for example, at page 3, lines 4-20. Claims 17-40 have been added by this amendment. Support for new claims 17-40 is found throughout the application, including, for example, page 3, line 22 – page 4, line 1; page 5, lines 8-9; page 6, lines 5-7; pages 8-9; page 13, lines 13-21; page 19, lines 8-18; page 22, page 66; pages 84-89; page90, lines 4-17; Example 5; Example 23; and claims 1-5, and 15 as originally filed.

No new matter has been added by these amendments. Furthermore, Applicants have enclosed another copy of the Mathur reference for the Examiner's review in light of these amendments, and specifically solicit any questions or comments the Examiner may have regarding the Mathur reference.

Rejection under 35 U.S.C. § 112, ¶ 1

Claims 1-16 were rejected as not enabled by the specification. In particular, the Office Action asserts that the specification "does not reasonably provide enablement for the generic class of polymers having an ester or amide bond." Office Action at 2. The Office Action further asserts that the present specification "offers only relatively narrow guidelines in making and using only one class of nucleophile, those used to construct PEG derivatives used as hydrogels." *Id.* In support of this rejection, the Office Action states that the art (Hern *et al.*, J. Biomed. Mater. Res. 39:266-76, 1998) "teaches that PEG has several properties which are essential for hydrogels. The compounds must not stick to cells, must be biodegradable, and must be able to be synthesized *in vivo*." *Id.* The Office Action concludes that:

> Lacking any further guidance from the specification the skilled artisan must perform the undue experimentation of developing synthesis protocols, testing cell adhesion, biodegradability etc. of the resulting polymers. Since the claims are not limited to uses of any kind, the skilled artisan must also uncover a reasonable use for these compounds.

Id. Applicants respectfully traverse this rejection.

Applicants respectfully assert that all pending claims are fully enabled by the specification. As an initial matter, Applicant note that the pending claims are directed to a biomaterial including an ester or amide bond to a pharmaceutically active moiety, where the bond has a certain half life, as well as methods of making and administering such biomaterials. As the specification states:

> Pharmaceutically active compounds can contain a variety of chemical groups, some of which are nucleophilic and some of which are electrophilic. In terms of drug stability, highly reactive groups are typically undesirable, and thus highly reactive groups are rarely found on pharmaceutically active compounds. Many examples of pharmaceutically active compounds can be found that do not contain nucleophilic groups other than alcohols. The reactivity of these alcohol groups is generally so low that coupling the pharmaceutically active compound to a material is challenging. Long reaction times would be required, and any competing reactions would be very problematic because purification of a pharmaceutically active compound-polymer complex would be very difficult. The separation techniques that are commonly used in chemistry were developed for relatively small molecules and are not very effective with polymers due to their high molecular weight. The greater purity that can be obtained for a pharmaceutically active moiety coupled to a linker compared to a polymer coupled to a linker is important for the clinical use of precursor components or biomaterials made from these compounds since the remaining impurities could cause undesired side-effects in mammals. Thus, several advantages can be gained by converting a single alcohol on the pharmaceutically active compound to a thiol or amine using a linker. In the case of oligonucleotides or peptides, this may be quite simple, since the thiol containing group can be easily added during the synthesis of the molecule. In the case of organic molecules, this requires more effort, but is often feasible. Modifications to the synthesis of a particular pharmaceutically active compound, especially one that has already passed government regulatory approval, is highly undesirable. Preferably, any modification performed to couple a pharmaceutically active compound to a biomaterial is done in such a way that the original pharmaceutically active compound is eventually regenerated by the hydrolysis of the ester or amide bond onto the pharmaceutically active moiety. Because some pharmaceutically active compounds retain their therapeutic activity after modification of a reactive group, such as an alcohol or amine, biomaterials that release compounds with such modifications can also be therapeutically useful.

Page 85, line 24 – page 87, line 3.

Methods of making biomaterials containing an ester or amide bound to a pharmaceutically active compound are exhaustively described in the specification. For example, the specification states:

> The current invention converts an alcohol or amine on the pharmaceutically active compound to a more reactive thiol or amine group. Because of the superior nucleophilicity of the thiol group as compared with an amine group and because amine groups are often found on pharmaceutically active compounds, a linker containing a thiol group is preferred over one containing an amine group. In some instances, however, the presence of an amine instead of a thiol in the linker may give a more desirable rate of release of the pharmaceutically active compound. The methods described herein include adding a linker molecule to the pharmaceutically active compound, rather than to the biomaterial or polymer. The chemical nature of this linker molecule can be quite diverse, but consists of the general structure R_1-COOH before reaction with the pharmaceutically active compound, where R_1 is an organic moiety that does not contain a substantially nucleophilic or electrophilic group. This carboxylic acid containing molecule is then condensed with an alcohol or amine from the pharmaceutically active compound. In one case, a poorly reactive sulfur or nitrogen atom is contained within the R_1 group, and by the use of suitable deprotection chemistries a free thiol or amine can then be generated. In another case, R_1 is CH2=CH-, which can be reacted with a second linker molecule of the structure R_2-SH or R_2-NH_2. A poorly reactive sulfur or nitrogen atom is included in R_2, and by the use of suitable deprotection chemistries a free thiol or amine can then be generated. The attachment of the linker molecule is then followed by extensive purification, which would not be possible if the pharmaceutically active compounds were directly attached to a biomaterial or polymer. Additionally, the attachment of such linkers can be incorporated into the overall synthesis of a pharmaceutically active compound, rather than occurring after the complete synthesis of the compound. Additionally, new pharmaceutically active compounds can be designed, based on the structures of existing pharmaceutically active compounds, that are more easily attached to a polymer using the methods described herein, but which have similar pharmacokinetics to the original compound.

Page 87, line 4 – page 88, line 6.

In addition, the specification teaches:

> In one method of the invention, a pharmaceutically active compound whose nucleophilic character consists of the presence of amines, alcohols, or weaker nucleophiles, is reacted so that the amine groups are protected against further reaction using standard techniques. An alcoholic group on the protected pharmaceutically active compound or a pharmaceutically active compound containing only alcoholic reactive groups is targeted for further reaction with a derivative of mercaptopropionic acid or mercaptoacetic acid in which the mercapto group is protected or aminopropionic acid or glycine in which the amine group is protected. An ester linkage is formed by condensing the carboxylic acid in the protected thiol or amine-containing compound acid with the alcohol on the pharmaceutically active compound. The protecting group on the amine or mercapto group and the protecting groups, if any, on the pharmaceutically active moiety are then removed using standard techniques. This product is then reacted with a water-soluble polymer containing conjugated unsaturated groups as described in more detail below. In a related method, a pharmaceutically active compound containing a free primary or secondary amine can be reacted as described above to form an amide-containing compound that can be attached to a polymer.

Page 88, line 10 – page 89, line 1.

As concerns the Hern reference, Applicants first note that the reference is concerned only with the formation of hydrogels through photopolymerization, *i.e.*, free radical initiated polymerization. As such, Hern is reporting the properties of the hydrogels prepared by photopolymerization. In particular, Hern *et al.* state, at page 266, that:

> Polyethylene glycol (PEG) has been employed as a biomaterial because of its remarkable nonadhesivity towards proteins and, hence, toward cells.
>
> * * *
>
> PEG diacrylate hydrogels adhere to tissue surfaces upon which they are polymerized, presumably by flow of precursor into tissue texture or by diffusion of precursor into the extracellular matrix to form, after polymerization, either mechanical interdigitation or an interpenetrating polymer network, respectively. The polymerized hydrogels are relatively nonadhesive to cells at the free surface, however, presumably due to poor protein adsorption to the hydrophilic, nonionic material surface.

Applicants respectfully submit that the Hern reference does not support the proposition in the Office Action that "PEG has several properties which are <u>essential</u> for hydrogels." Office Action at 2 (emphasis added). If the Examiner believes that some other passage from the Hern reference supports this proposition, Applicants respectfully

request that the Examiner provide Applicants with that specific text. Rather, Applicants submit that the Hern reference merely acknowledges that adhesive peptides may be incorporated into non-adhesive PEG hydrogels. This is but one aspect of the present invention. As explained in Applicants' specification:

> One strong benefit of the use of the addition reactions described herein is that other bioactive biofunctional groups can be incorporated into the biomaterial, for example, to provide sites for binding of adhesion-promoting receptors on the cell surface or sites for growth factor binding.

Page 80, lines 13-16. Applicants further describe "a variety of adhesion-promoting peptides" which may be used in accordance with the method of the invention. Page 80, lines 19-23; *see also* Table 4 and SEQ ID NOS: 39-49. Applicants also teach that:

> One can incorporate peptide sites for cell adhesion, namely peptides that bind to adhesion-promoting receptors on the surfaces of cells into the biomaterials of the present invention. It is straightforward to incorporate a variety of such adhesion-promoting peptides, such as the RGD sequence from fibronectin or the YIGSR sequence from laminin. As above, this can be done, for example, simply by mixing a cysteine-containing peptide with PEG diacrylate or triacrylate, PEG diacrylamide or triacrylamide or PEG diquinone or triquinone a few minutes before mixing with the remainder of the thiol-containing precursor component. During this first step, the adhesion-promoting peptide will become incorporated into one end of the PEG multiply functionalized with a conjugated unsaturation; when the remaining multithiol is added to the system, a cross-linked network will form. Thus, for example, when an adhesion peptide containing one cysteine is mixed with a PEG triacrylate (at, e.g., 0.1 mole of peptide per mole of acrylate end group), and then a protease substrate peptide containing two cysteine residues is added to form the three-dimensional network (at, e.g., equimolar less 0.1 mole peptide per mole of acrylate end group), the resulting material will be highly biomimetic: the combination of incorporated adhesion sites and protease sites permits a cell to establish traction in the material as it degrades a pathway for its migration, exactly as the cell would naturally do in the extracellular matrix *in vivo*. In this case, the adhesion site is pendantly incorporated into the material. One could also incorporate the adhesion site directly in to the backbone of the material. This could be done in more than one way. One way would be to include two or more thiols (e.g., cysteine) in the adhesion peptide or protein. One could alternatively synthesize the adhesion peptide (e.g., using solution phase chemistry) directly onto a polymer, such as PEG, and include at least one thiol (e.g., cysteine) or conjugated unsaturation per chain end.

Page 46, line 17 – page 47, line 17. In addition to the foregoing, the present application contains twenty-five examples which provide the skilled artisan with abundant guidance to make and use the invention as presently claimed.

Finally, the Office Action asserts that because "the claims are not limited to uses of any kind, the skilled artisan must also experiment to uncover a reasonable use for these compounds." Office Action at 2. To the extent the Office Action seeks utility for the subject matter of the pending claims, Applicants refer the Examiner to the section of the specification entitled, "Biomedical Applications for Hydrogels," page 50, line 15 – page 52, line 20, and respectfully submit that this section provides a sufficient number of uses for the invention as claimed. Furthermore, Applicants respectfully submit that it is unnecessary to limit any of the pending claims to "uses of any kind."

For all the foregoing reasons, Applicants respectfully submit that the rejection of the pending claims under 35 U.S.C. § 112, ¶ 1 should be withdrawn. Far from performing undue experimentation, the skilled artisan need only read Applicants' specification to determine appropriate synthetic protocols, cell adhesion, and biodegradability of the resulting biomaterials. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 1-16 were rejected under 35 U.S.C. § 103(a) as obvious in view of the Hern reference. In support of this rejection, the Office Action states:

> Hern teaches polymers having an ester or amide bond formed with nucleophiles comprising the groups recited in claim 5 and 12. See, for example, Hern, p. 266, 267, Fig. 1; p. 268, col. 2 p. 269, col. 2.
>
> The claims differ from Hern in the recitation "half-life of between 1 hour and one year." However, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use polymers having a half-life within this range because this is the common time period in which experiments are carried out.

Office Action at 3. Applicants traverse this rejection and respectfully submit that the Office Action does not establish a *prima facie* case of obviousness with respect to any of the pending claims.

As discussed above, Applicants' claimed invention is directed to a biomaterial including an ester or amide bond to a pharmaceutically active moiety, where the bond has a certain half life, as well as methods of making and administering such biomaterials. In contrast, Hern teaches the use of photopolymerization using cross-linking chemistries, *i.e.* linking a peptide via a primary amine to a polymer via an amine reactive N-hydroxysuccinimidyl ester, for tissue resurfacing. There is no mention – let alone teaching or suggestion – of <u>any</u> pharmaceutically active moiety in Hern. Rather, as the title of the reference implies, Hern is concerned with the incorporation of adhesion peptides into nonadhesive hydrogels useful for tissue resurfacing.

Moreover, contrary to the statement in the Office Action, Hern does not teach suggest, or disclose "polymers having an ester or amide bond formed with nucleophiles comprising the groups recited in claim 5 and 12." This is primarily because the coupling reaction in Hern is a condensation reaction, *not* an addition reaction. Furthermore, there is no mention of a "thiol" or any thiolated material in Hern. And, as the Office Action recognizes, Hern is completely silent with respect to the half-life recitation in Applicants' claimed invention. Applicants further submit that the unsupported generalization in the Office Action that "this is the common time period in which experiments are carried out" is irrelevant to the half-life of a bond recited in the claimed invention, and would remain irrelevant, even if supported by a reference.

Accordingly, for all the foregoing reasons, Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness of the pending claims in view of Hern.

CONCLUSION

Applicants submit the pending claims are in condition for allowance and respectfully request prompt and favorable action. Enclosed is a check in the amount of $460.00 and a petition to extend the period for replying for three months, to and including October 25, 2001. If an interview with Applicants' attorney would expedite prosecution, the Examiner is invited to call the undersigned at 617-428-0200.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: October 25, 2001

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21559
PATENT TRADEMARK OFFICE

50154.003001 Reply to OA dated 4.25.01

Version with Markings to Show Changes Made

Specification page 57, line 20 – page 58, line 3:

Michael-type addition to conjugated unsaturated groups can take place in good to quantitative yields at room or body temperature and in mild conditions with a wide variety of nucleophiles (Pathak, supra; ~~Mathur et al., Journal of Macromolecular Science Reviews In Macromolecular Chemistry and Physics," C36:405-430,1996;~~ Moghaddam et al., Journal of Polymer Science: Part A: Polymer Chemistry 31:1589-1597, 1993; and Zhao~~Zhoa~~, supra). Conjugated unsaturated groups, such as vinyl sulfones (Pathak, supra) ~~or acrylamides (Mathur, supra)~~, have been used to link PEG or polysaccharides to proteins through Michael-type reactions with amino- or mercapto-groups.

[1. A biomaterial comprising a pharmaceutically active moiety, wherein said biomaterial has an ester or amide bond onto said pharmaceutically active moiety, said bond having a half-life of between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 C.]

[2. The biomaterial of claim 1, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 1 day and 9 months in an aqueous solution at pH 7. 4 and 37 C.]

[3. The biomaterial of claim 1, wherein said pharmaceutically active moiety is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.]

[4. The biomaterial of claim 1, wherein said organic molecule is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.]

5. (Amended) A biomaterial formed from the cross-linking of two or more precursor components, wherein at least one of said precursor components has[having] the formula:

$$D\text{-}Y\text{-}C(O)\text{-}(CH_2)_n\text{-}S\text{-}(CH_2)_2\text{-}COX\text{-}P,$$

D-Y-C(O)-$(CH_2)_n$-NH-$(CH_2)_2$-COX-P,
D-Y-C(O)-$(CH_2)_n$-NH-U-P,
D-Y-C(O)-$(CH_2)_n$-S-U-P,
D-Y-C(O)-$(CH_2)_2$-S-L-S-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-S-L-S-U-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-S-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-S-U-P,
D-Y-C(O)-$(CH_2)_2$-S-L-NH-CH_2-CH_2-CO-X-P,
D-Y-C(O)-$(CH_2)_2$-S-L-NH-U-P,
D-Y-C(O)-$(CH_2)_2$-NH-L-NH-CH_2-CH_2-CO-X-P, or
D-Y-C(O)-$(CH_2)_2$-NH-L-NH-U-P,

wherein D is a pharmaceutically active moiety; n is 1 or 2; Y is O, NH, or N; L is a linear or branched linker; X is O or N; P is a water-soluble polymer or a water-swellable polymer comprising one or more conjugated unsaturated groups; and U is the product of the addition of a nucleophile to an electrophilic group that is attached to said polymer[; wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 C].

7. (Amended) The biomaterial of claim 5, wherein said cross-linking occurs in the presence of a [linker] polymer comprising two or more nucleophilic groups[, wherein said linker provides targeting to a cell, tissue, organ, organ system, or site within a mammal].

11. (Amended) The biomaterial of claim 5, wherein said [linker comprises]cross-linking occurs in the presence of a molecule comprising an adhesion site, growth factor binding site, protease binding site, or enzymatically degradable site, and further comprises at least one strong nucleophile or a conjugated unsaturated group.

12. (Amended) The biomaterial of claim 7[5], wherein said [linker comprises a] nucleophilic groups are selected from the group consisting of thiols and amines[that increases the rate of release of a pharmaceutically active compound having the formula D-OH, D-NH_2, or D-NH by reacting with the ester or amide bond onto D].

15. (Amended) A method of treating or preventing a disease, disorder, or infection in a mammal by administering to said mammal a biomaterial comprising a pharmaceutically active moiety, wherein said biomaterial has an ester or amide bond onto said pharmaceutically active moiety, said bond having a half-life of between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.

17. (New) The biomaterial of claim 5, wherein said pharmaceutically active moiety is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

18. (New) The biomaterial of claim 5, wherein said pharmaceutically active moiety is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

19. (New) The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

20. (New) The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

21. (New) The biomaterial of claim 5, wherein the half-life of the ester or amide bond onto said pharmaceutically active moiety is between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

22. (New) The method of claim 13, wherein said pharmaceutically active compound is derived from one of the group consisting of synthetic organic molecules, naturally

occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

23. (New) The method of claim 13, wherein said pharmaceutically active compound is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

24. (New) The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.

25. (New) The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

26. (New) The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

27. (New) The method of claim 13, wherein the precursor component includes an ester or amide bond with a half-life between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

28. (New) The method of claim 15, wherein said pharmaceutically active moiety is derived from one of the group consisting of synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, biosynthetic proteins or peptides, naturally occurring peptides or proteins, and modified naturally occurring peptides or proteins.

29. (New) The method of claim 15, wherein said pharmaceutically active moiety is paclitaxel, doxorubicin, 5-fluorodeoxyuridine, estradiol, 2-methoxyestradiol, or a derivative thereof.

30. (New) The method of claim 15, wherein the bond has a half-life between 1 day and 9 months in an aqueous solution at pH 7.4 and 37 °C.

31. (New) The method of claim 15, wherein the bond has a half-life between 2 days and 6 months in an aqueous solution at pH 7.4 and 37 °C.

32. (New) The method of claim 15, wherein the bond has a half-life between 4 days and 3 weeks in an aqueous solution at pH 7.4 and 37 °C.

33. (New) A pharmaceutically active compound of the formula $D\text{-}O_2C\text{-}(CH_2)_n\text{-}SH$ or $D\text{-}N(O)C\text{-}(CH_2)_n\text{-}SH$, wherein n is 1 or 2 and D is a pharmaceutically active moiety.

34. (New) The pharmaceutically active compound of claim 33 further comprising at least one polymer cross-linked to the pharmaceutically active compound by a conjugated addition reaction between a thiol group of the pharmaceutically active compound and a conjugated unsaturated group of the polymer.

35. (New) A method of forming a biomaterial, said method comprising the steps of:

(a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound;

(b) coupling the thiol, amine in said linker or incorporated into said pharmaceutically active compound to a polymer comprising two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component; and

(c) cross-linking the uncoupled conjugated unsaturated groups in one or more said precursor components.

36. (New) The method of claim 35, wherein said cross-linking occurs at or near a site within the body of a mammal.

37. (New) A method of forming a biomaterial, said method comprising the steps of

(a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound;

(b) coupling the thiol or amine in said linker or incorporated into said pharmaceutically active compound to at least a first polymer comprising two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component;

(c) providing at least a second precursor comprising nucleophilic groups; and

(d) cross-linking the conjugated unsaturated groups of the precursor of step b) to the nucleophilic groups of the precursor of step c) by a conjugated addition reaction.

38. (New) The method of claim 37, wherein said cross-linking occurs at or near a site within the body of a mammal.

39. (New) The method of claim 38, wherein said mammal is a human.

40. (New) A method of treating or preventing a disease, disorder, or infection in a mammal by administering to said mammal a biomaterial comprising a pharmaceutically active moiety, wherein said biomaterial has an ester or amide bond onto said pharmaceutically active moiety, said bond having a half-life of between 1 hour and 1 year in an aqueous solution at pH 7.4 and 37 °C.